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Original Article

The risk factors of mitral insufficiency recurrence after coronary artery bypass grafting with or without mitral valve repair in patients with ischemic cardiomyopathy

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Abstract

Aim: This study aimed to identify risk factors for mitral insufficiency (MI) recurrence after isolated coronary artery bypass grafting (CABG) and for CABG with mitral valve (MV) repair of moderate MI in patients with ischemic cardiomyopathy.

Material and Methods: This is a single-centre prospective study. We included 76 patients with moderate MI and poor left ventricular function (EF <35%). The patients underwent isolated CABG or CABG with MV repair. The age of the patients was 57±8 years, and 90% were men. MV repair was restricting annuloplasty using a rigid ring with a size of 26–30.

Results: The total complications in the long-term period were 19 (52.7%) and 8 (23.5%) in the isolated CABG and CABG + MV repair groups, respectively (p=0.015). After isolated CABG in patients suffering ischemic cardiomyopathy (IC) and moderate MI, progression of MI (grade 3) initially 0%, after 12 months, 31%, after 36 months, 71%, p <0.001 is observed.

Conclusion: Isolated CABG or CABG with MV repair in patients with IC does not result in a significant decrease in MI in the long-term, when compared with the baseline. The revealing of the predictors of the progression of MI made it possible to determine the threshold values of the performance indicators of MV repair and assisted with the determination of the surgical treatment strategies for patients with moderate MI.

Keywords: Ischemic cardiomyopathy, mitral insufficiency, coronary artery bypass grafting

INTRODUCTION

The presence and severity of MI is an unfavourable predictor in patients with left ventricular (LV) systolic dysfunction after acute myocardial infarction and chronic ischemia (1).

MI progresses due to fibrosis of the papillary muscles in IC, causing severe MI in postinfarction dysplasia. This results in valve failure and also LV remodelling, increased cavity size and sphericity (2). Due to the deformation of the LV cavity, the distance from the base of the papillary muscle to the fibrous ring of the mitral valve (MV) increases, the ring is stretched along the posterior semicircle, and the distance between the bases of the papillary muscles is increased. MV repair for ischemic MI (IMI) can improve MI using annuloplasty (3). However, in contrast with the organic lesion of MV, valve annuloplasty using a ring of smaller diameter is not a physiological correction because it restores leaflet coaptation without eliminating the cause of excess leaflet tension (4). Hung et al (2004) investigated the association of recurrent regurgitation with annuloplasty (5). They showed that recurrent regurgitation in the MV was associated with further tension of the mitral leaflets, due to the progression of LV remodelling (6).

Currently, there is no consensus on the need for correcting moderate IMI with severe systolic dysfunction of the LV and LV ejection fraction (LVEF) <35%. Due to the complex multicomponent mechanism of IMI formation and LV remodelling processes in IC, defining surgical strategies is difficult. Thus, isolated CABG has a

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lower risk of perioperative complications and mortality, but does not eliminate MI; thus, it does not reduce the influence of MI on further cardiac remodelling. Subsequently, the MV repair should be as safe and effective as possible, considering the severity of patients suffering with IC. The improvement of life quality and the longevity of patients may not occur without IMI correction in patients suffering with severe LV dysfunction, provided that the patency of the coronary arteries is restored. Data on the effect of combined interventions on the development of heart failure (HF) are conflicting, and options for postoperative LV remodelling and the determining factors have been insufficiently studied (7). The validity of the additional intervention in the MV with an insignificant and moderate IMI remains a subject of discussion (8).

This study aimed to compare the surgical correction results for isolated CABG and for CABG in combination with MV repair for moderate MI in patients with IC and to identify the risk factors determining MI return.

MATERIAL AND METHODS

This was a prospective, single-centre, open- label, randomised controlled trial to compare the surgical correction results for isolated CABG and for CABG in combination with MV repair for moderate IMI in patients with IC and to identify the risk factors determining MI return. Participants were randomly allocated preoperatively in a 1:1 ratio (Figure 1).

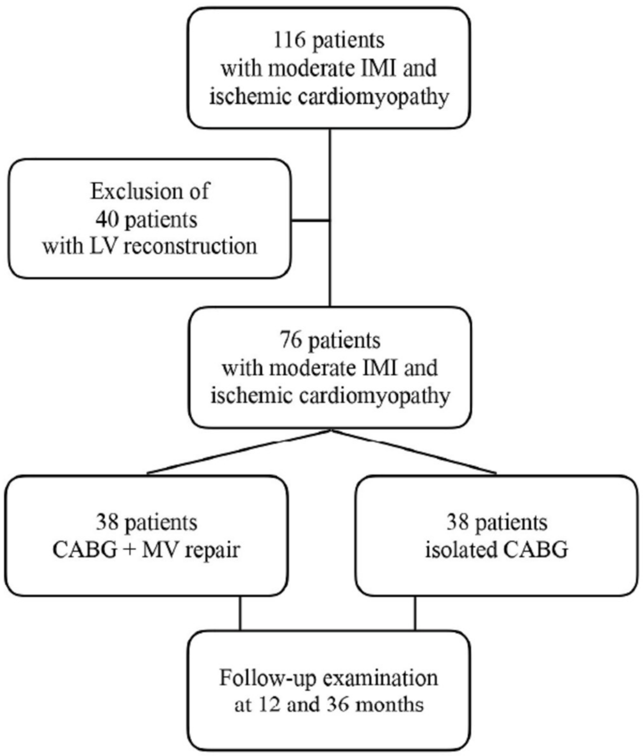

Figure 1: Study design

The study was approved by the institutional review board of the National Medical Research Centre named after academician E.N. Meshalkin. Written informed consent was obtained from eligible patients, who agreed to participate in the study. This study included 76 patients with IC and moderate MI and LVEF <35% who did not undergo LV reconstruction. The criteria stipulated that all subjects were above 18 years, suffering from coronary artery disease (CAD), LVEF <35%, and moderate IMI.

The exclusion criteria were acute MI, cardiogenic shock and aortic valve damage requiring surgical correction, organic MV damage, and pathology of other organs and systems in the terminal stage. Before surgical treatment, patients were divided into two groups: isolated CABG (control) and CABG with MV repair (studied). Before the surgery, prior to discharge, and at 12 and 36 months postoperatively, the patients underwent follow-up examinations, including general clinical examination, echocardiography (EchoCG), and a six-minute walk test (SMWT).

The mean age of the patients was 57±8 years (range, 30–75 years), and 90% were men. The basic demographic data of patients are presented in Table 1.

All surgical procedures were performed under the conditions of cardiopulmonary bypass with standard cannulation of the ascending aorta and right atrium (in the control group) or bicaval cannulation (in the studied group). A custodiol solution was used to protect the myocardium during ischemia of the heart. Both arterial and venous grafts were used to revascularise the myocardium. In 95% of cases, the left internal thoracic artery was used to bypass the anterior descending artery, and arterial grafts were unused in only four (5%) cases, due to the poor quality of the internal thoracic artery.

Isolated annuloplasty was used with a rigid support ring with a ring size of 26–30 to correct MI. All patients before and after surgery received standard medical therapy for CAD and HF in the postoperative period; patients from the group with MV surgery additionally received anticoagulants for six months after surgery.

Statistical Analysis

The statistical processing of the data was performed using the program STATISTICA (StatSoft, USA). Comparative analysis was performed using nonparametric methods, which do not require normal distribution. Descriptive characteristics were presented as mean±standard deviation for normally distributed data, median (first quartile; third quartile) for abnormally distributed numeric data, percentage (95% confidence interval (CI) lower bound, 95% CI upper bound) for categorical data, with CI calculation using the Wilson formula.

RESULTS

The mean duration of clamping of the aorta in the isolated CABG was 48±18 mins and 131±29 mins ($p<0.001$) in the CABG group in combination with the MV repair.

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Table 1. Preoperative characteristics of patients included in the study

Indicator		CABG group n=38 (50%)	CABG + MV repair group n=38 (50%)	Difference, MED (95% confidence interval)	P-value
Male		34 (89.4%)	30 (78.9%)	0.4 (0.1; 1.9)	.346
Female		4 (10.6%)	8 (21.1%)	2.2 (0.5;11.2)	.346
Age		58±5	58±7	0 (–4; 4)	.913
Chronic renal failure		2 (5.2%)	7 (18.4%)	4 (0.7;42.2)	.153
Myocardial infarction		37 (97.3%)	37 (97.3%)	1 (0.1; 14.5)	>.999
Hypertensive disease		29 (76.3%)	30 (78.9%)	1.1 (0.4; 3.7)	>.999
Diabetes mellitus		8 (21.0%)	7 (18.4%)	0.8 (0.2; 3.1)	>.999
Atrial fibrillation		6 (15.7%)	10 (26.3%)	1.9 (0.5; 7.2)	.399
Stroke		2 (5.2%)	4 (10.5%)	1.5 (0.2;19.4)	>.999
Functional class of HF, NYHA classification	I, n	0	0	–	>.999
	II, n	5 (13.2%)	4 (10.5%)	1.3 (0.3; 7.1)	>.999
	III, n	22 (57.9%)	25 (65.8%)	0.7 (0.3; 2.0)	.637
	IV, n	11 (28.9%)	9 (23.7%)	0.7 (0.3; 2.0)	.795
Angina pectoris grade, the Canadian Cardiovascular Society Classification	Without angina	8 (21%)	8 (21%)	1.0 (0.3; 3.5)	>.999
	I, n	4 (10.5%)	5 (13%)	0.8 (0.1; 4.0)	>.999
	II, n	12 (31.5%)	12 (31.5%)	1.0 [0.3; 2.9)	>.999
	III, n	11 (29%)	11 (29%)	1.0 (0.3; 3.0)	>.999
	IV, n	3 (7.9%)	2 (5.2%)	1.5 (0.2;19.4)	>.999

In the early postoperative period, all patients were observed in the intensive care ward for 2–7 days. To compare the frequency of occurrence of any complication in the two groups, a combined point was evaluated whereby all complications of the early postoperative period were considered. No significant statistical difference was found between the groups; hence, complications were noted in 16 (42.11%) and 18 (74.36%) patients in the first group and second group, respectively (p>0.899).

Hospital mortality in the isolated CABG and CABG + MV repair groups was 2 (5.4%) and 4 (10.81%), respectively (p=0.675). In the first group, respiratory failure affected 11 (29.73%) patients, and in the second group 10 (26.3%), (p = 0.727), and HF - 4 (10.8%) cases in the control group and 6 (15.7%) in the studied group (p = 0.651), with one pacemaker implantation due to sinus node dysfunction (2.7%) in the CABG group and two (5.4%) due to an atrioventricular block after surgery in CABG+MV repair group, (p=0.654). Severe HF was the cause of mortality during the postoperative period for most patients.

In the long-term follow-up period of three years postoperatively, significant complications were stroke, sudden death, progressive HF, and MV dysfunction (separation of the support ring) after MV annuloplasty (Table 2). The total complications in the long-term period were 19 (52.7%) and 8 (23.5%) in the first group and second group, respectively (p=0.015) (Table 2).

Table 2. Complications in the long-term postoperative period

Complication	**CABG n=36 (50%)**	**CABG + MV repair n=36 (50%)**	**CABG/ CABG + MV repair Risk ratio**	**P-value**
Stroke	4 (11.1%)	0	8.5	.115
Sudden cardiac death	4 (11.1%)	1 (2.9%)	3.78	.358
Heart failure	11 (44%)	5 (14.7%)	2.08	.157
Detachment of the annuloplastic ring	0	4 (11.7%)	–	.051
Combined points	19 (52.7%)	8 (23.5%)	2.24	.015

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Amongst the severe complications in the comparison groups, progression of HF was noted, which led to a fatal outcome in five (14.7%) and 11 (44%) patients in the CABG + MV repair and isolated CABG groups, respectively (p=0.157). The progression of MI in four (11.7%) patients with the annuloplasty ring detachment (p=0.051) was noted in the CABG + MV repair group in the long-term period. Two of these patients underwent a reoperation to correct MI, and two were included in the waiting list for heart transplantation, due to worsening HF and a reduction of LV contractility.

The cumulative survival rate, depending on the method of surgical correction, is shown in Figure 2. A significant difference in survival between the two groups (45% and 74%, respectively; equating to a log rank test of p=0.037) was seen, with no significant differences between the groups being identified during two years of follow-up. After one and two years postoperatively, the survival rate was 84% and 78%, and 84% and 71%, with MV repair and CABG, respectively. After three years, the survival curves diverged, with a significant difference between the groups. In the Cox model, for the survival of groups receiving isolated CABG and CABG + MV repair, the ratio of mortality risks in groups is 0.457 with a standard error of 0.385 (p=0.04). The Cox model indicated a significant 0.457 times lower risk of death in the CABG + MV repair group than that in the isolated CABG group (Figure 2).

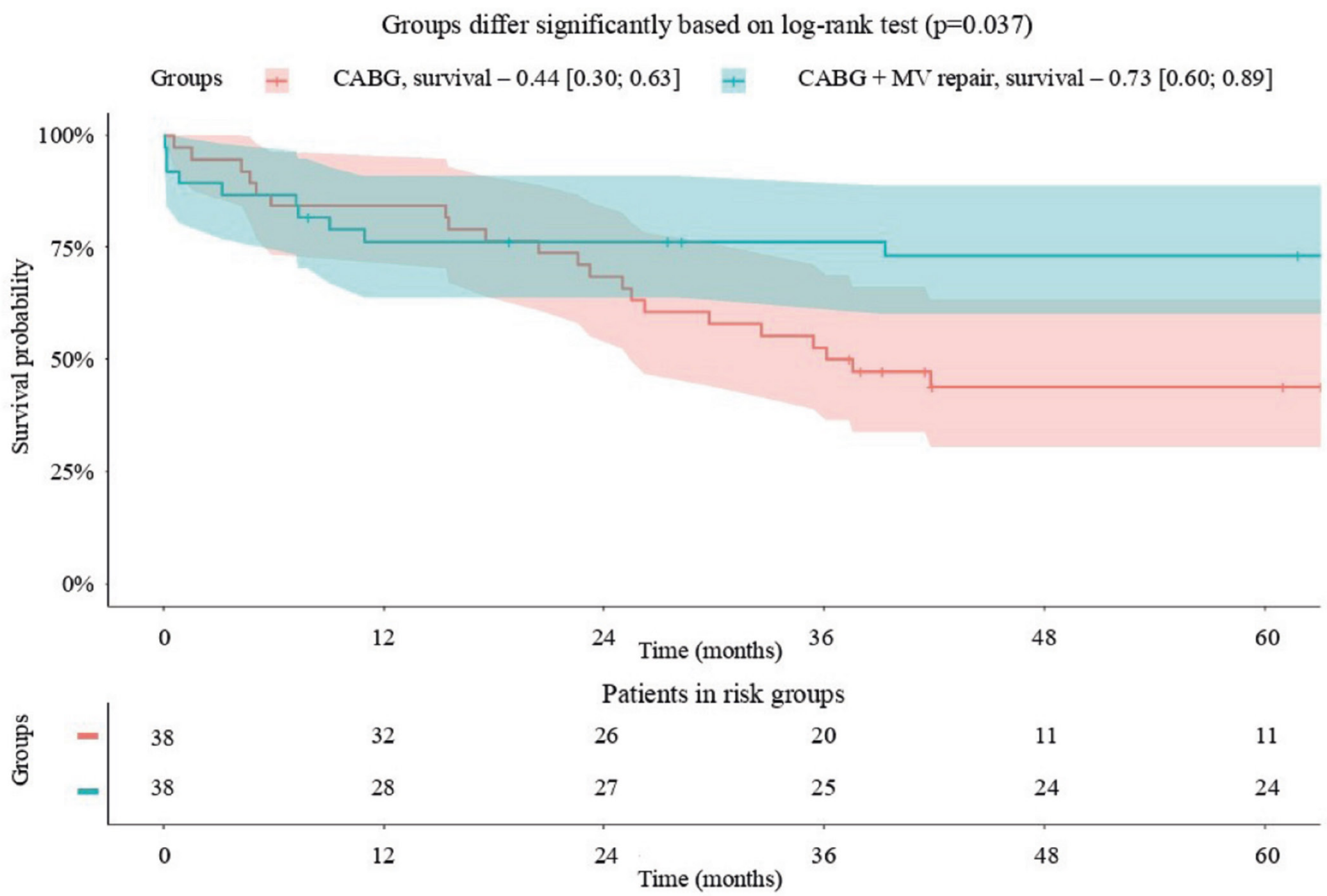

Figure 2: Survival of patients with moderate IMI and IC, depending on the method of treatment

Dynamics of the Long-Term Clinical and Functional State of Patients in the Two Groups

More than half of the patients in both groups suffered with angina pectoris grades II and III preoperatively and 12 months postoperatively, and both groups showed a significant movement of >80% of patients to grade I or a complete relief of the symptoms of angina pectoris. Tolerance to exercise was also assessed using the SMWT. A significant improvement in exercise tolerance postoperatively in both groups was shown. Thus, the mean distance of the SMWT increased from 280–420m and from 303–510m in the control group (p=0.01) and the studied group, respectively (p<0.001), 12 months postoperatively. This dynamic of tolerance to physical activity coincides with the improvement of the functional class of HF one year postoperatively.

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After CABG, improvement of LV contractility was noted in the CABG + MV repair group. Thus, in the studied group, LVEF increased from 31.5% (24.75%; 34%) to 33% (28%; 38%) 12 months postoperatively and remained above the baseline values for up to 36 months of follow-up (p<0.001). Isolated CABG also leads to an increase in the mean LVEF in the postoperative period, but tends to decrease significantly during distant periods of observation. Thus, LVEF increased from 31.5% (27.75%; 34%) to 33% (27%; 37.25%) 12 months postoperatively (p=0.02), and 30% (24%; 32%) 36 months postoperatively, thereby demonstrating no significant difference when compared with the baseline (p=0.23). In the first 12 months after surgery, most patients in both groups had a significant increase in LVEF. Negative dynamics were detected after three years, when LVEF dropped to baseline values.

Dynamics of Ischemic Mitral Insufficiency

The study analysed the MI dynamics, depending on the treatment method for patients suffering with IC (Figures 3). The criteria for assessing the degree of MI were effective regurgitation opening (ERO), percentage of regurgitating jet, and width of the regurgitation opening.

The isolated CABG in patients suffering with ischemic heart disease (IHD) and severe systolic dysfunction did not lead to a decrease in MI during the follow-up period of 12 months. MI progressed significantly after isolated CABG. In relation to patients in the CABG + MV repair group, MI decreased to 0–1 mitral regurgitation grade after 12 months.

Dependence on the method of treatment was shown after performing a comparative analysis of the dynamics of the MI grade during the observation period up to 12 months. Thus, positive MI dynamics, that is, a decrease by one or more grades, was detected in all patients in the CABG + MV repair group and in 28% in the isolated CABG group, with MI progression occurring in 31% of cases. During examination after 36 months in both groups, progression of MI grade was observed. After 36 months in the CABG + MV repair group, patients had positive dynamics of 47%, progression to MI grade 2 in 32% of cases, and an increase in MI above grade 2 MI in 21% of cases. On average, MI after isolated CABG remained without dynamics at 12 and 36 months. In the CABG + MV repair group, the mean positive dynamics were noted only 12 months postoperatively and became the same in 36 months.

Before surgery on both groups, MI was of grade 2, and the groups did not differ significantly. However, 12 months postoperatively, significant differences in the MI grade in the isolated CABG group were noted 12 months postoperatively compared with the CABG + MV repair group (p<0.01). Analysis of the MI grade in the long-term also demonstrated a significant difference between the groups. Thus, MI was statistically significantly less than in the isolated CABG group 36 months postoperatively in the CABG + MV repair group (chi-square=2.286; p<0.01).

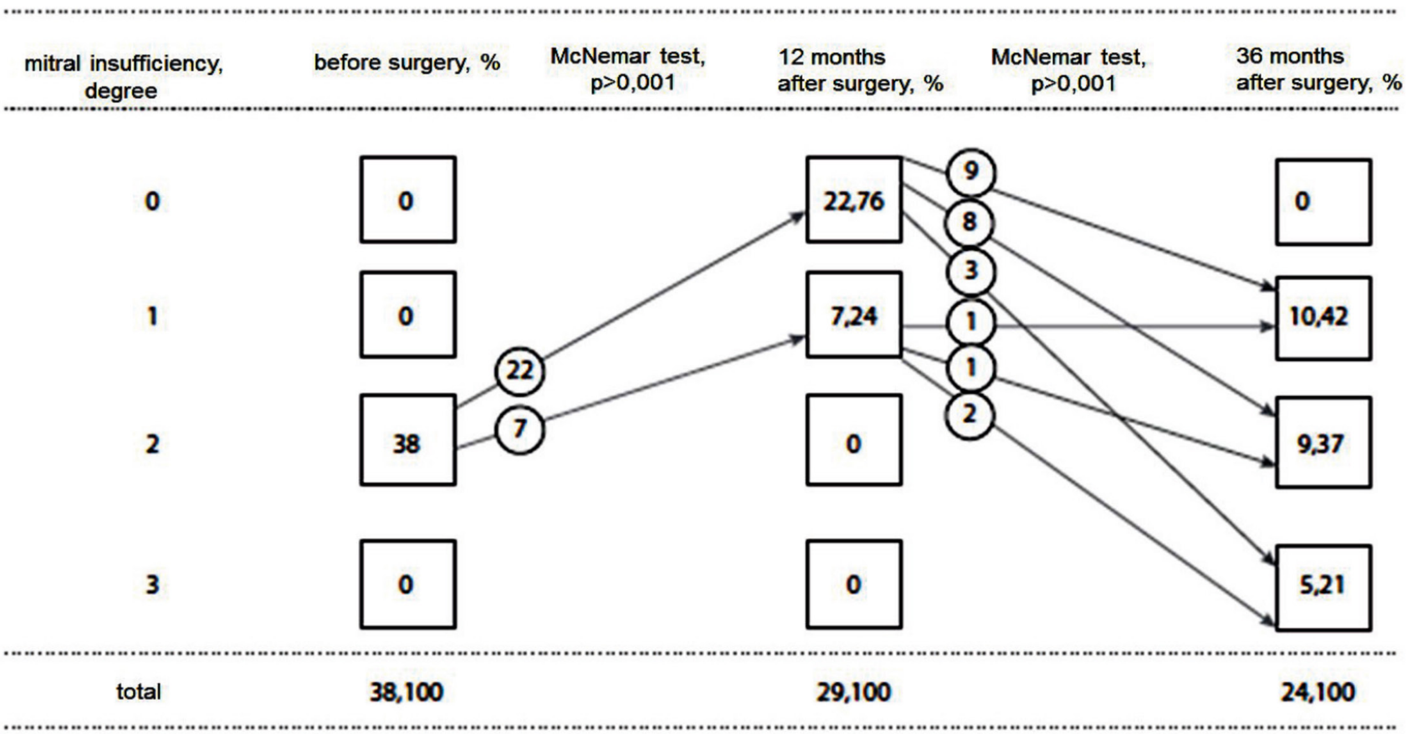

Figure 3: Dynamics of MI in the CABG group

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A significant advantage in the dynamics of the degree of MI amongst the groups of CABG + MV repair was found, when compared with isolated CABG. Thus, after isolated CABG in patients with IC and moderate MI, progression of MI (grade 3 MI, initially 0%; after 12 months, 31%; after 36 months, 71%; p <0.001) was observed, even with initially moderate changes in the geometry of the MV.

The initial echocardiographs (EchoCGs) of LV and MV were analysed to identify the causes of MI progression in IC over a long-term postoperative period. The analysis was performed for all surviving patients of each group exhibiting negative MI dynamics during the 12 and 36 months postoperatively. Using the single-factor logistic regression model, significant predictors of MI progression were volume LV indices (EDI, ESI, EDV, and ESV) in both groups (Table 3). However, the evaluation of predictors in the multivariate regression model, in addition to the significant ESI, also revealed significant predictors of MV remodelling (IPD, PAD, and leaflet coaptation depth) (Table 4).

From the regression analysis, the progression of MI in IC was noted to have a credible relationship to global postinfarction remodelling of the heart. Concurrently, LV volume indices, total LVEF, and the restrictive type of diastolic dysfunction have a significant predictor role. Thus, the MV geometry and function are dependent on the geometry and function of the basal part of the LV (basal remodelling).

The threshold changes in the rates of MI progression were assessed to build the algorithm of surgical strategies in the treatment of patients with moderate IMI and IC. Thus, the model predicts effective repair in patients with the following predictor values: ESI <70 ml/m^2, LVEF>30%, ERO<0.3 cm^2, IPD<45 mm, PAD<55 mm, coaptation depth>7 mm, diastolic dysfunction not of a restrictive type, and pressure in the PA<45 mm Hg.

Table 3. Model of univariate long-term logistic regression of the risk of MI progression

Predictors	Odds ratio MI/no MI	95% odds ratio CI	p-value
EDI	1.042	(1.003; 1.097)	0.06
ESI	10.49	(1.006; 1.109)	**0.04**
EDV	1.021	(1.005; 1.047)	**0.03**
ESV	1.025	(1.005; 1.055)	**0.03**
EF	0.885	(0.746; 1.03)	0.12
S MR/S LA	1.052	(0.901; 1.253)	0.52
ERO	0.187	(0; 33929.04)	0.84
MV fibrous ring diameter	1.094	(0.837; 1.465)	0.51
S leaflet tension	0.441	(0.038; 4.226)	0.48
IPD in diastole	1.033	(0.943; 1.145)	0.48
PAD	0.965	(0.862; 1.074)	0.51
Coaptation depth	1.009	(0.63; 1.629)	0.96
Disfunction type	1.285	(0.241; 7.208)	0.76
Right atrium	0.752	(0.267; 2.009)	0.57
Coaptation length	0.941	(0.422; 2.064)	0.87
Diastolic LV dysfunction, initial	1.308	(0.383; 4.805)	0.66
Left atrium	1.864	(0.45; 9.351)	0.40
LA pressure	0.991	(0.918; 1.066)	0.80
Tricuspid regurgitation	0.484	(0.085; 2.249)	0.36

Abbreviations: EDI = end-diastolic index; ESI = end-systolic index; EDV = end-diastolic volume; ESV = end- systolic volume; S MR\S LA = ratio of the area of mitral regurgitation to the area of the left atrium; IPD = interpapillary distance; PAD = papillary-annular distance; PA = pulmonary artery

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Table 4. Model of long-term multifactor logistic regression and risk of progression of MI

Predictors	Odds ratio MI/no MI	95% odds ratio CI	p-value
ES	1.043	(0.929; 1.206)	**0.04**
EF	0.845	(0.529; 1.173)	0.06
ERO	2824675.838	(0; +∞)	0.16
IPD in diastole	1.223	(0.905; 1.822)	**0.05**
PAD	0.680	(0.293; 1.17)	0.07
Coaptation depth	0.891	(0.226; 5.182)	**0.05**
Diastolic LV dysfunction	1.166	(0.152; 8.664)	**0.04**
PA pressure	0.990	(0.876; 1.14)	0.06
Tricuspid regurgitation	4.784	(0.424; 215.478)	0.166

Note: + ∞ denotes values >106, the deviance of the constructed model is 25.057 for 21 degrees of freedom. Abbreviations: EDI = end-diastolic index; ERO = effective regurgitation aperture; IPD = interpapillary distance; PAD = papillary-annular distance; PA = pulmonary artery

DISCUSSION

For a long time, IMI correction by the supporting annuloplastic ring, combined with CABG, was considered an effective surgical procedure (9). However, the results of MV repair with severe insufficiency and the results of isolated CABG with moderate MI with LVEF <35% were disappointing in the long-term (10,11). Thus, with the annuloplasty of severe MI, the percentage of return of regurgitation remains high, and MI progresses with isolated CABG (12,13). The reason for ineffective surgical treatment for this pathology is due to the complex mechanism of MI formation and ischemic LV remodelling, combined with severe systolic dysfunction. In addition, the risk of perioperative complications and lethality increases with the expansion of the volume of surgery by MV repair compared with isolated CABG.

Statistical differences between the comparison groups were obtained regarding the assessment of long-term survival (73% in the CABG + MV repair and 44% after isolated CABG graft p =0.037). Simultaneously, up to three years of observation, statistically significant differences were not observed, but there was a tendency indicating the advantages of MV repair in combination with CABG, when compared with isolated revascularisation. The difference between the groups in terms of long-term survival is consistent with the 2014 metaanalysis of the differences between CABG and CABG + MV repair, following five years of follow-up after surgery (13). Estimated survival in our study was between surgical treatment groups with a LV EF of less than 35%, so the study by DJ Mauro confirms our thesis on the progression of HF and MI in IC (14). Perhaps this difference in the results of the study in survival is due to the fact that moderate ischemic MI in patients with low LV contractility makes a more significant contribution to hemodynamics than for moderately reduced LV functions. Perhaps annuloplasty of the MV 'opens' a vicious cycle of HF failure pathogenesis in patients with IC, which leads to improved survival in the long-run.

Based on our study, in both groups for patients with IHD and severe systolic LV dysfunction, there is no significant decrease in MI in the long-term, when compared with the baseline. However, the degree of MI after CABG + MV repair is lower than the initial values, unlike isolated CABG, when assessed 12 months postoperatively. In the observation period, up to 36 months, the MI degree after isolated CABG corresponded to the initial values. The determination of predictors in the progression of IMI in IC made it possible to determine the threshold values of the performance indicators of MV repair, and the evaluation of EchoCG predictors for annuloplasty preoperatively assisted with selection of the surgical treatment strategies of patients with IC and moderate MI.

LIMITATIONS

The present study aimed to optimize the selection of the most appropriate surgical treatment of patients with moderate MI with IC. The patients were selected according to clear criteria to ensure homogeneity of the groups, which serves to place limitations on the application of the results to the general population of patients with IMI. In the study, the selected patients had IHD and low LVEF, and the degree of MI was evaluated as moderate for all, whereas excluded patients had organic lesions of MI and aneurysms of LV, if aneurysm resection was shown in conjunction with LV repair.

There were no differences in the number of early postoperative complications and hospital mortality between groups, possibly due to the fact that the calculation of the sample was undertaken according to long- term survival, and the number of patients was insufficient to assess complications.

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Implantation of cardioverter-defibrillator (ICD) was not performed on patients in either group during hospitalisation because there was no clear guidance for ICD implantation in patients with IHD and LVEF <35% at the time of planning and patient selection in the international recommendations for treatment of HF.

CONCLUSION

Correction of IMI in patients with IC does not increase the number of complications in the early postoperative period, when compared with the group of isolated CABG. At the same time, in the long-term period, the number of complications in the CABG + MV repair group is significantly less than in the isolated CABG group (8 vs. 19, respectively, p=0.015).

MV repair leads to an improvement in the course of HF and LV remodelling indicators in the first year postoperatively (class NYHA III– IV preoperatively, 85%; after 12 months, 29%, p=0.003), but regression of the indicators 36 months postoperatively is noted (class NYHA III–IV preoperatively, 83%; after 36 months, 67%; p=0.386).

After isolated CABG in patients with IC and moderate MI, progression of MI (grade 3 mitral regurgitation, initially 0%; after 12 months, 31%; after 36 months, 71%; p <0.001) is observed, even with initially moderate changes in the geometry of the MV.

Conflict of Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Association: This study is not associated with any thesis or dissertation work.

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